NX-5948, a brain-penetrant BTK degrader with clinical activity in B-cell malignancies including CNS lymphoma

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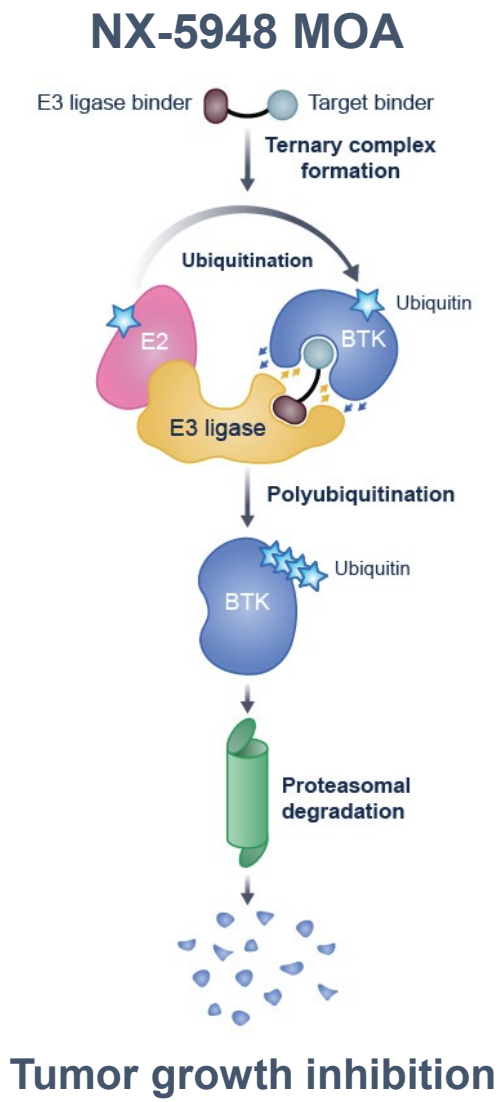
Nurix Is Advancing a Pipeline of Propriety and Partnered Programs in Oncology and Inflammation & Immunology

MOA	Oncology program	Target	Therapeutic area	Discovery – Lead Op	IND enabling	Phase 1a	Phase 1b
TPD	NX-2127	BTK-IKZF	B-cell malignancies				
	NX-5948	BTK	B-cell malignancies				
TPE	NX-1607	CBL-B	Immuno-Oncology				
TPD	Multiple	Undisclosed	Undisclosed				
	Multiple	Undisclosed	Undisclosed				GILEAD
	Multiple	Undisclosed	Undisclosed				sanofi
DAC	Multiple	Undisclosed	Oncology				Pfizer

MOA	I&I program	Target	Therapeutic area	Discovery – Lead Op	IND enabling	Phase 1a	Phase 1b
TPD	NX-5948	BTK	Inflammation / autoimmune				
	NX-0479 / GS-6791	IRAK4	Rheumatoid arthritis and other inflammatory diseases				GILEAD
	Multiple	Undisclosed	Inflammation / autoimmune				sanofi

TPD: Targeted Protein Degradation; **TPE**: Targeted Protein Elevation; **DAC**: Degrader Antibody Conjugate

Why Do We Need BTK Degraders?



BTK degraders can overcome treatment emergent resistance mutations

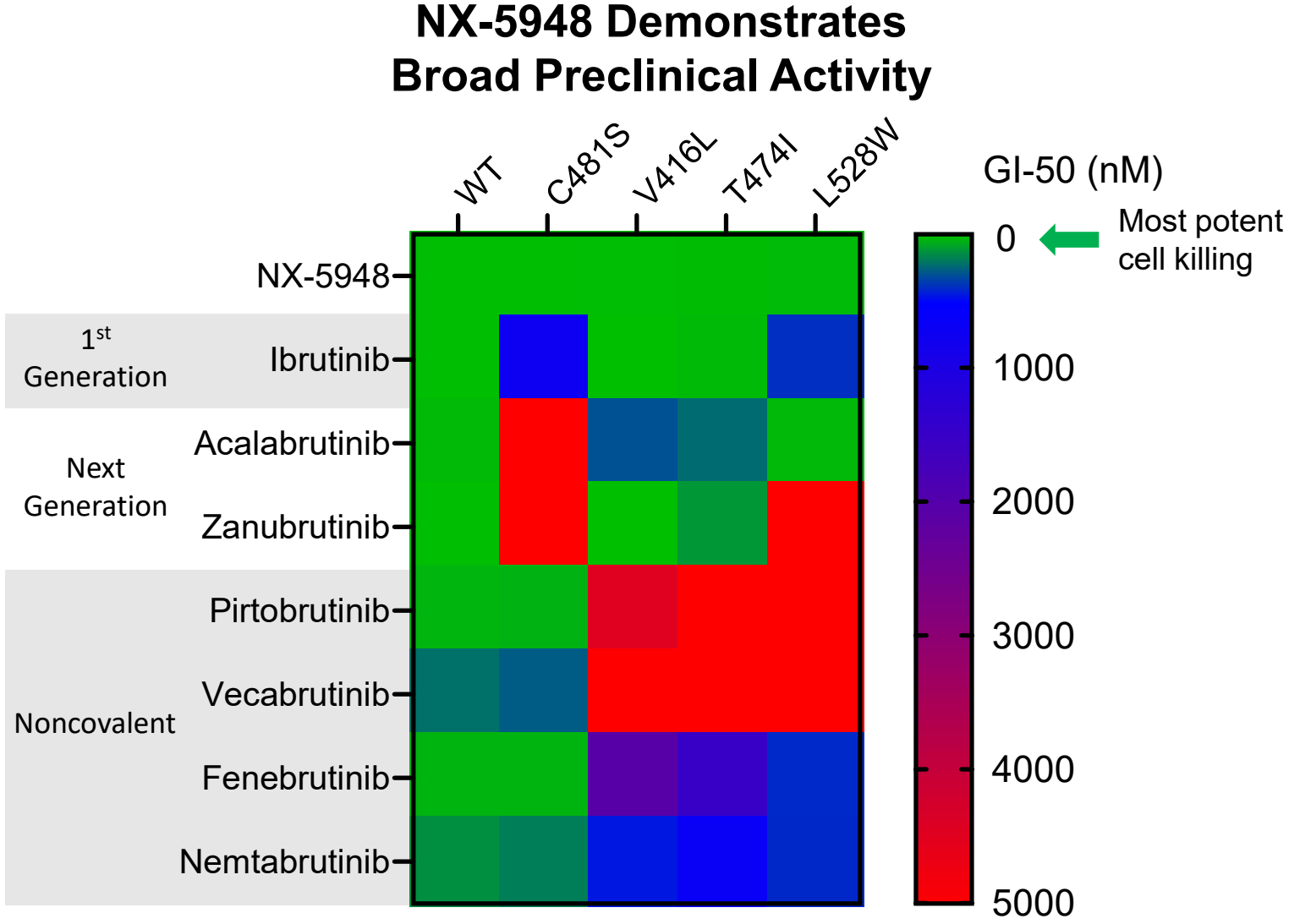
BTK degraders eliminate BTK scaffolding function

BTK degraders may be useful in a broader range of B-cell malignancies and autoimmune diseases

BTK degraders have the potential to displace inhibitors

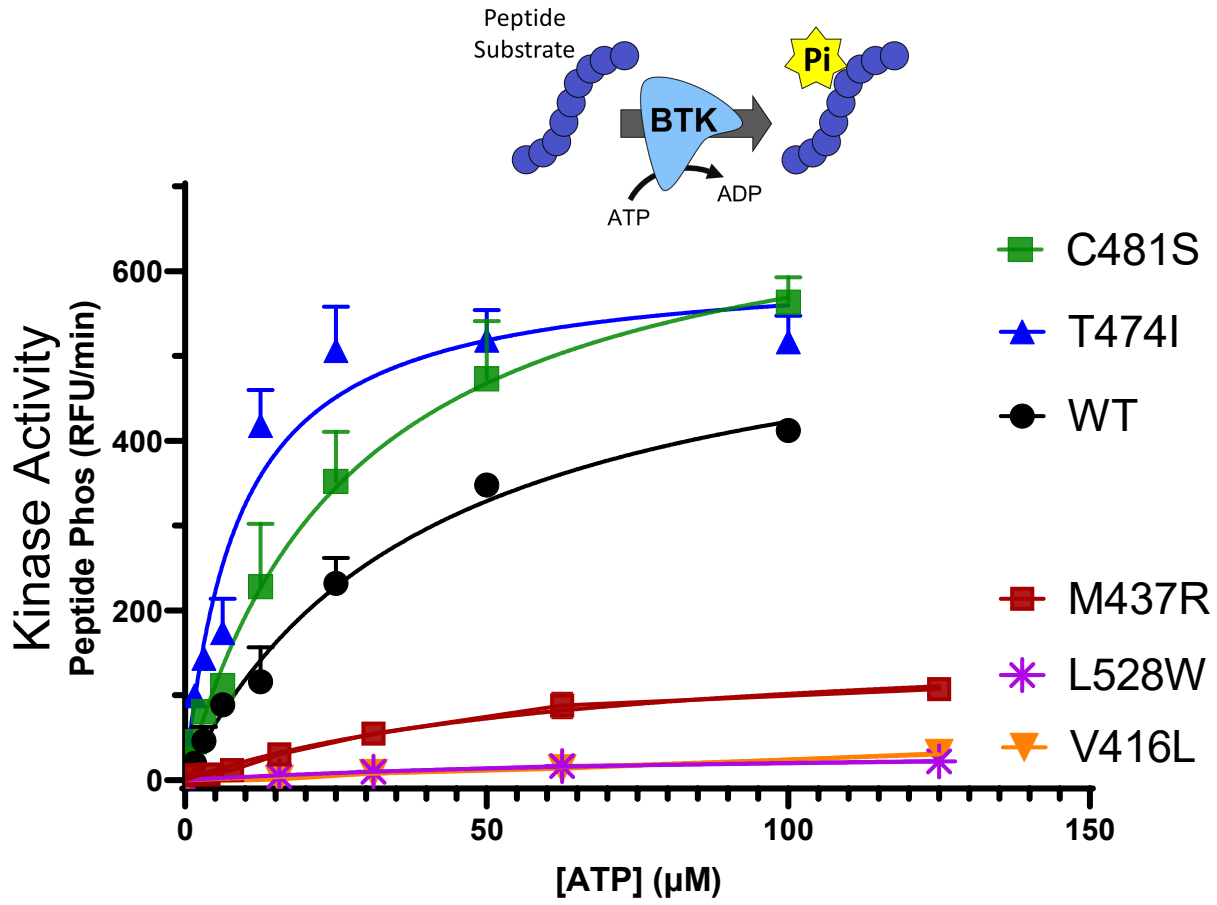
BTK Degraders Can Overcome Treatment Emergent Resistance Mutations

- All inhibitors have resistance mutation liabilities
- NX-5948 displays potent cell killing in the context of key resistance mutations
- We have shown that BTK degradation translates into clinical responses across mutation classes

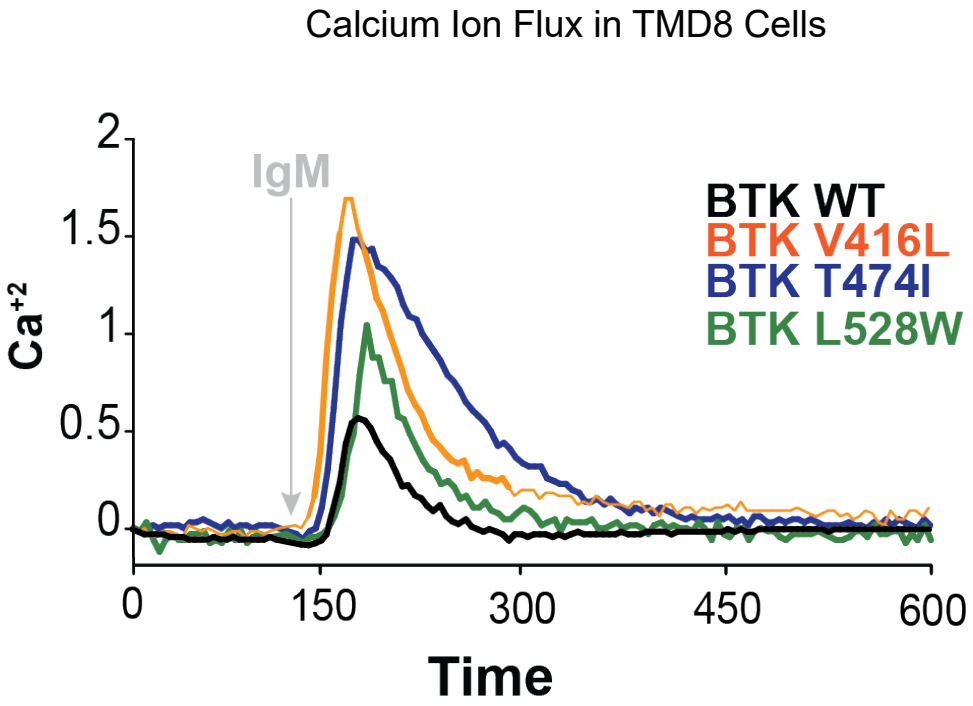


BTKi Resistant Mutations Lack Kinase Activity Yet Propagate BCR Signaling

BTKi-resistant mutations V416L and L528W lack kinase activity

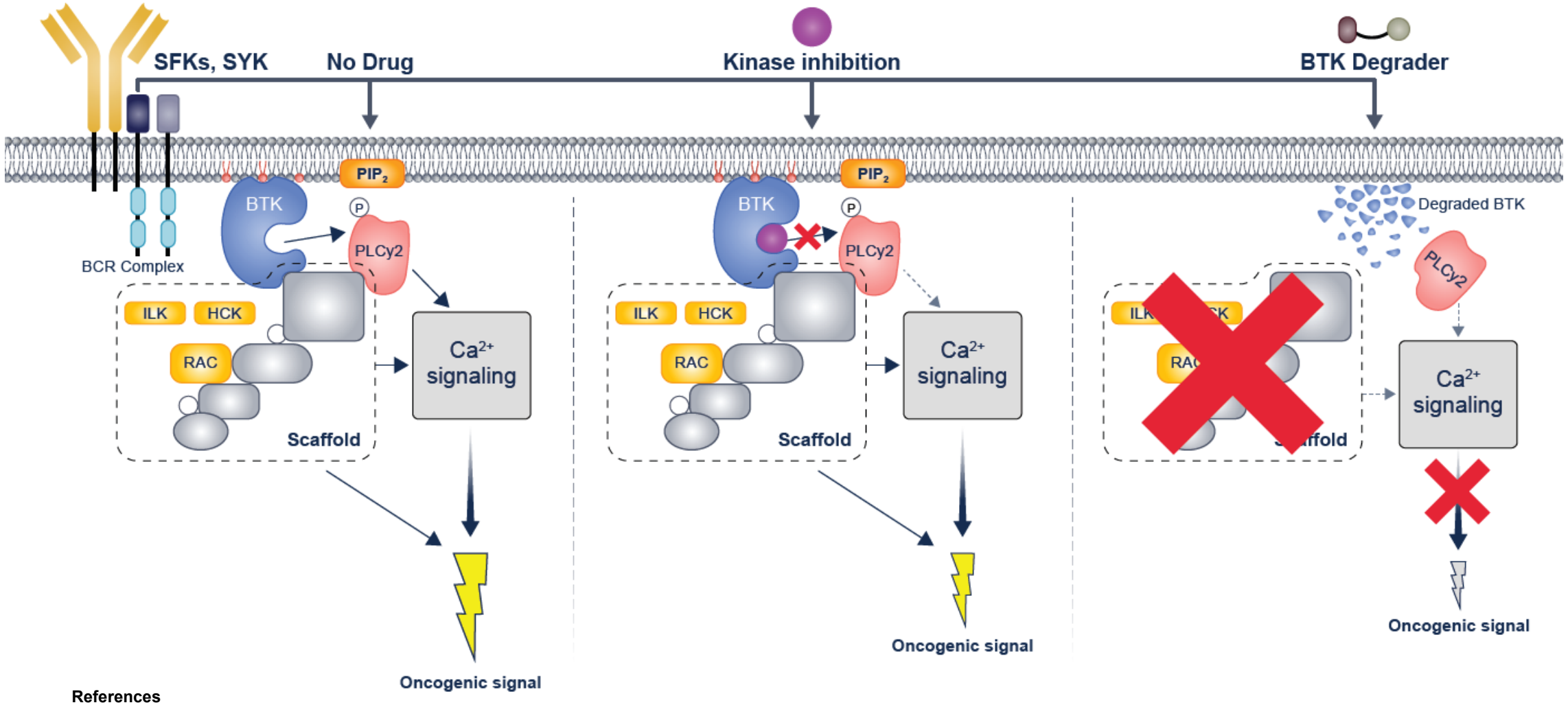


BTK kinase-dead mutants V416L and L528W propagate BCR signaling



Montoya et al., 2024, DOI: 10.1126/science.adi5798

BTK Degraders Disrupt BCR Signaling by Removing the Protein and All of Its Functions



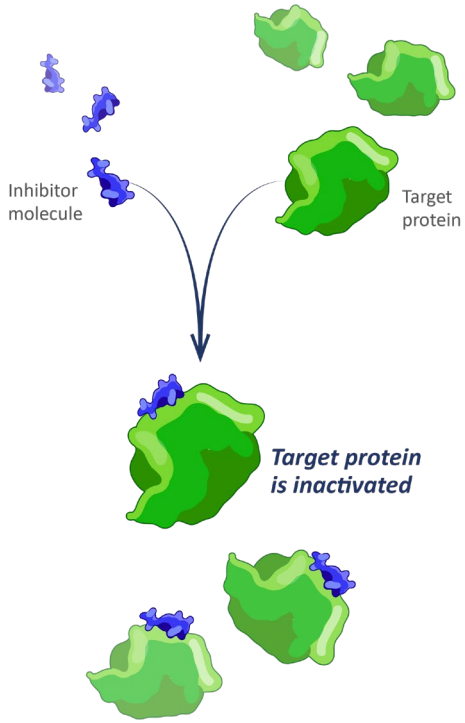
References

1. Montoya et al. Kinase-impaired BTK mutations are susceptible to clinical-stage BTK and IKZF1/3 degrader NX-2127. Science. 2024; 383
2. Eisen et al. Conditional Requirement for Dimerization of the Membrane-Binding Module of BTK. BioRxiv. January 17, 2024
3. Yuan et al. BTK kinase activity is dispensable for the survival of diffuse large B-cell lymphoma. J Biol Chem. 2022; 298 (11):102555

Degraders Are PK Advantaged Due to Their Catalytic Mechanism of Action

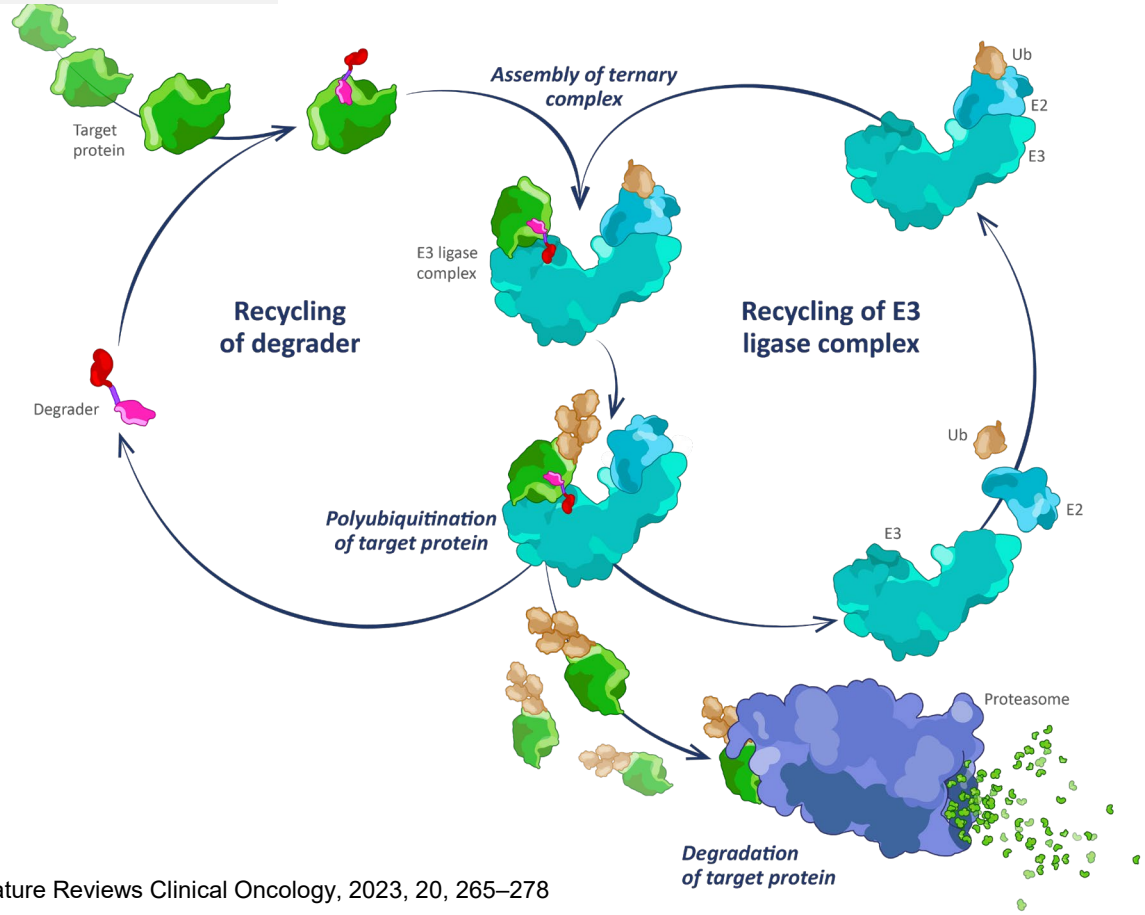
ONE inhibitor molecule inhibits ONE target protein

High levels of drug needed to maintain complete target coverage



ONE degrader molecule promotes degradation of MULTIPLE target proteins

Lower levels of drug needed to achieve complete target removal



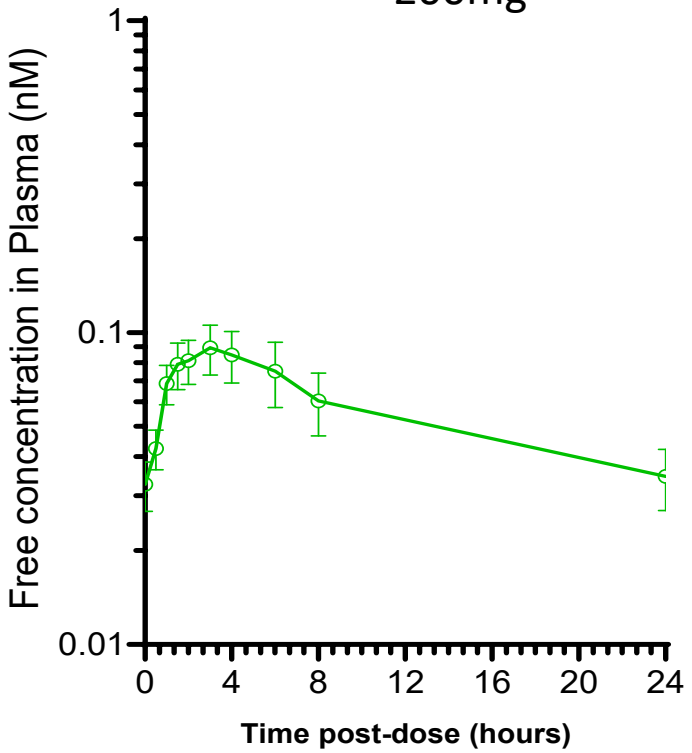
References

1. Chirnomas et al. Protein degraders enter the clinic — a new approach to cancer therapy. Nature Reviews Clinical Oncology, 2023, 20, 265–278

Clinically Active Doses of NX-5948 Show Lower Unbound Drug Exposure Than Covalent and Noncovalent BTK inhibitors

NX-5948 PK at steady state
Cycle 2 Day 1

200mg



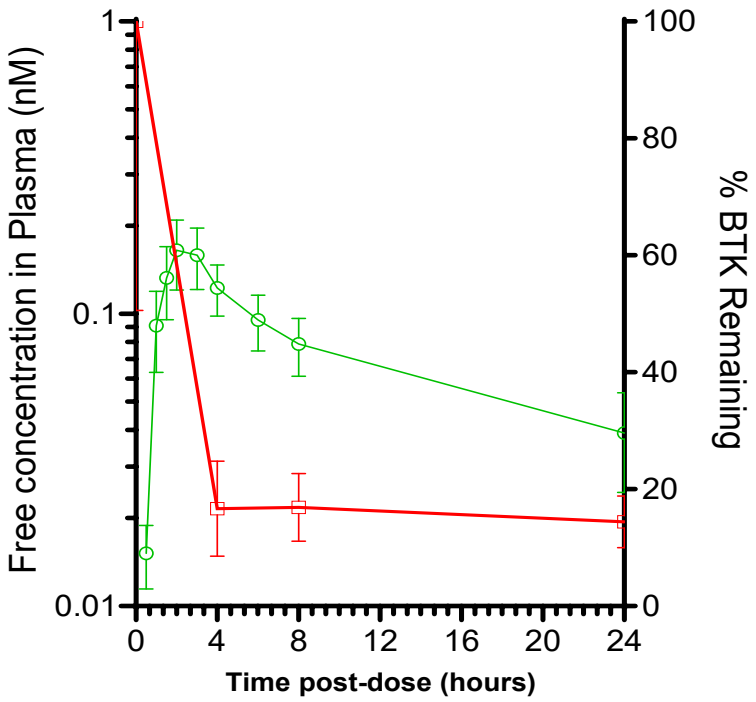
NX-5948 requires lower exposure than BTK inhibitors for clinical responses

	Ibrutinib (560mg QD)[1]	Zanubrutinib (160mg BID)[1]	Pirtobrutinib (200mg QD)[1]	NX-5948 (200mg QD)
$Cmax_{free}$ (nM)	8.0	40	540	0.09
$Cmin_{free}$ (nM)	0.2	3.5	250	0.03

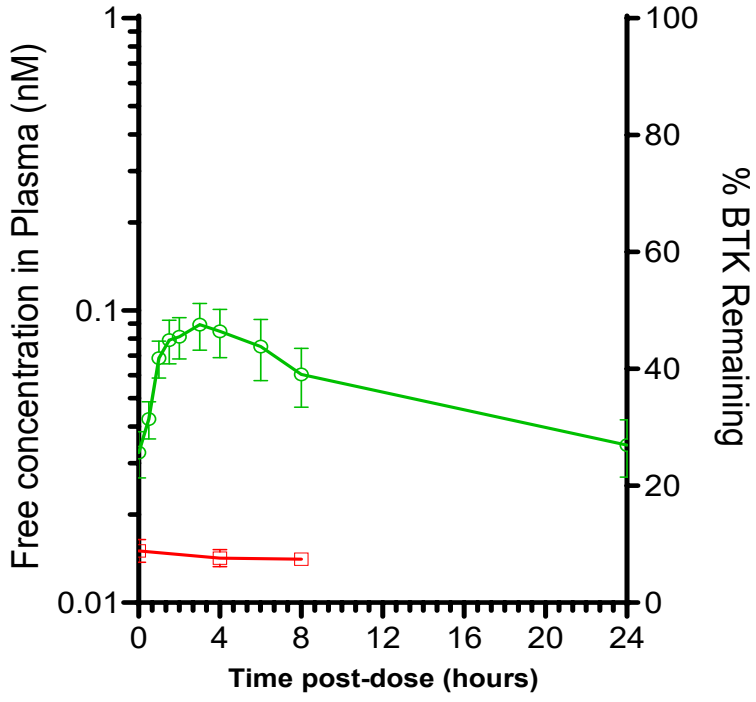
[1]clinically approved doses

NX-5948 Achieves Rapid, Significant and Sustained Target Degradation at Sub-Nanomolar Unbound Plasma Exposures

NX-5948 PK/PD
Cycle 1 Day 1

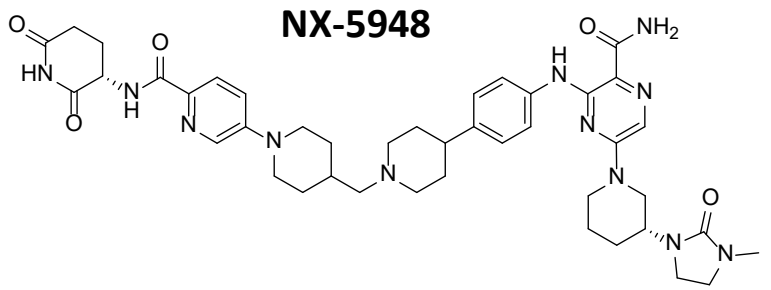


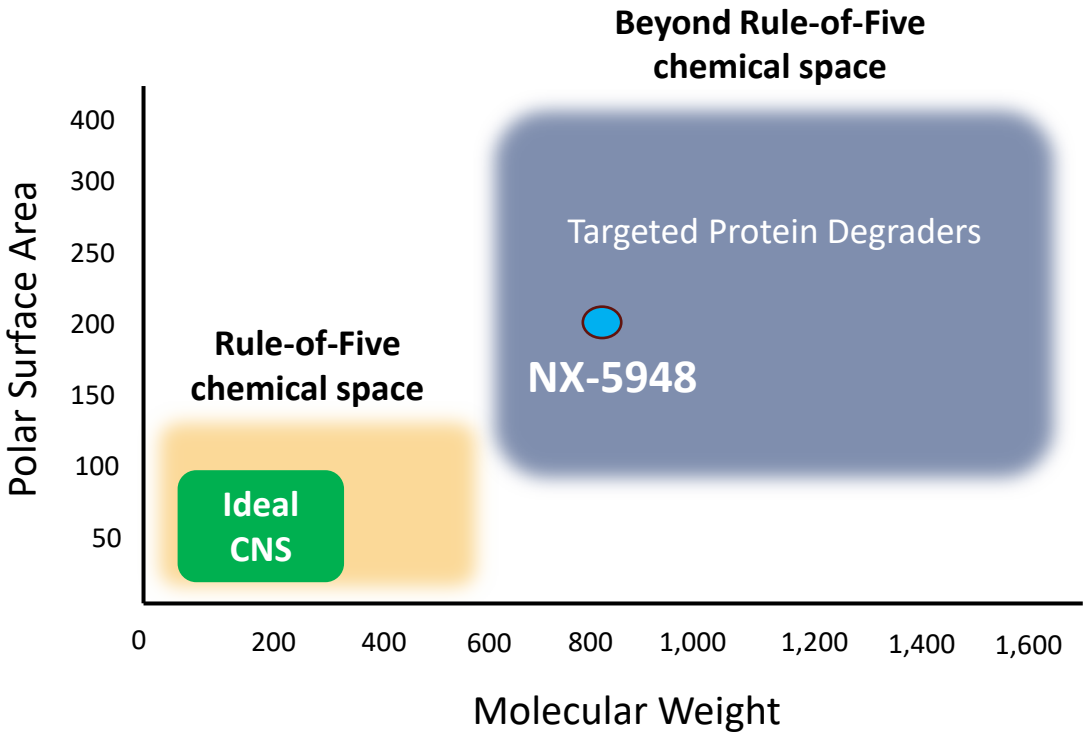
NX-5948 PK/PD
Cycle 2 Day 1



NX-5948 Exposure
% BTK Remaining

Established Metrics For Predicting CNS Penetration Suggest NX-5948 Unlikely to Achieve CNS Exposure





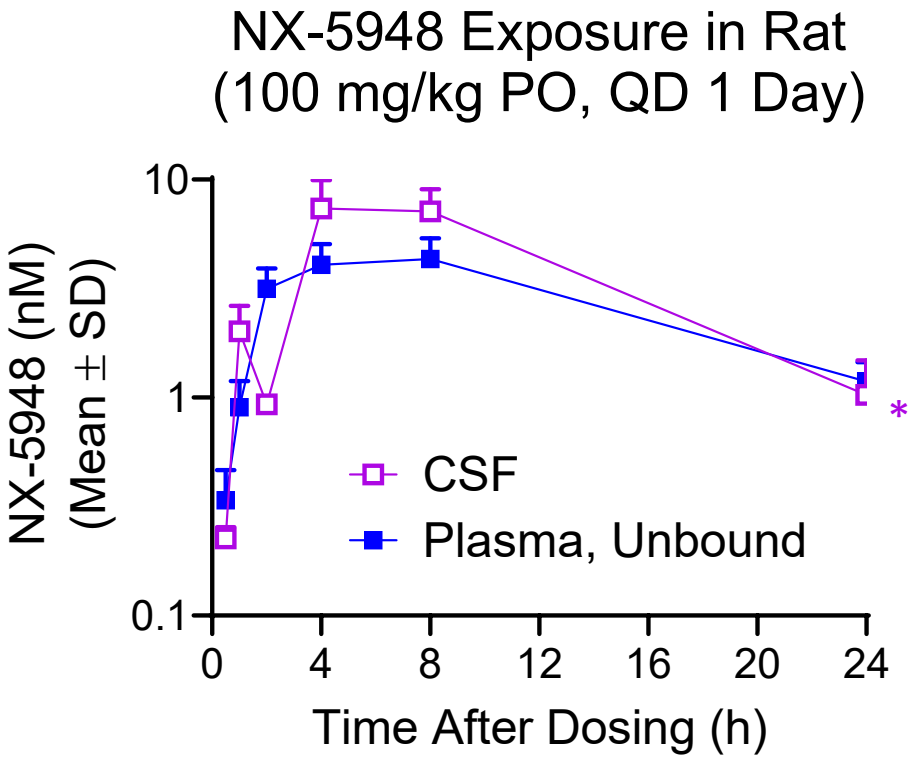
77% of marketed CNS drugs have an MPO score ≥ 4.0

Property	More Desirable*	Less Desirable	NX-5948 Property value	NX-5948 MPO score
ClogP	≤ 3	> 5	3.6	**0.7**
ClogD	≤ 2	> 4	0.9	**1.0**
MW	≤ 360	> 500	807	**0**
TPSA	40 to 90	≤ 20, > 120	202	**0**
HBD	≤ 1	> 4	5	**0**
pKa	≤ 8	> 10	9.1**	**0.45**
				Total = 2.2

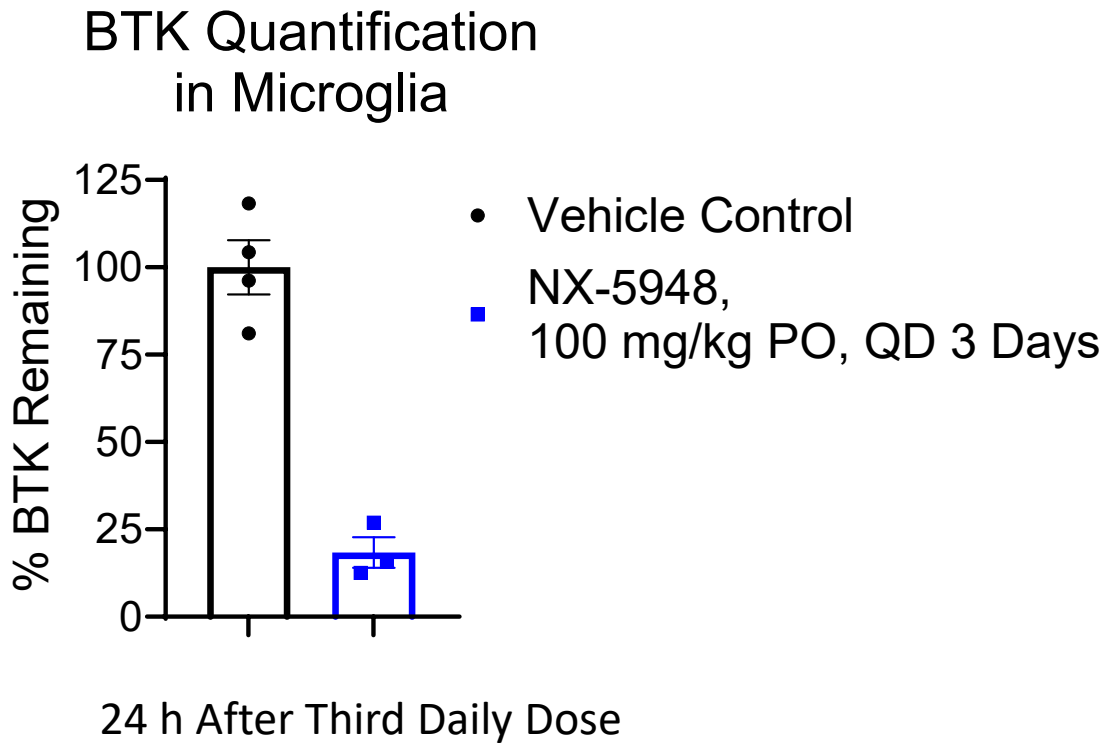
**Measured pKa

*Wager, et al., *ACS Chem Neuro*, 2016

Oral Dosing of NX-5948 in Rats Results in Similar CSF and Unbound Plasma Exposures, Translating to Effective Degradation of BTK in Microglia



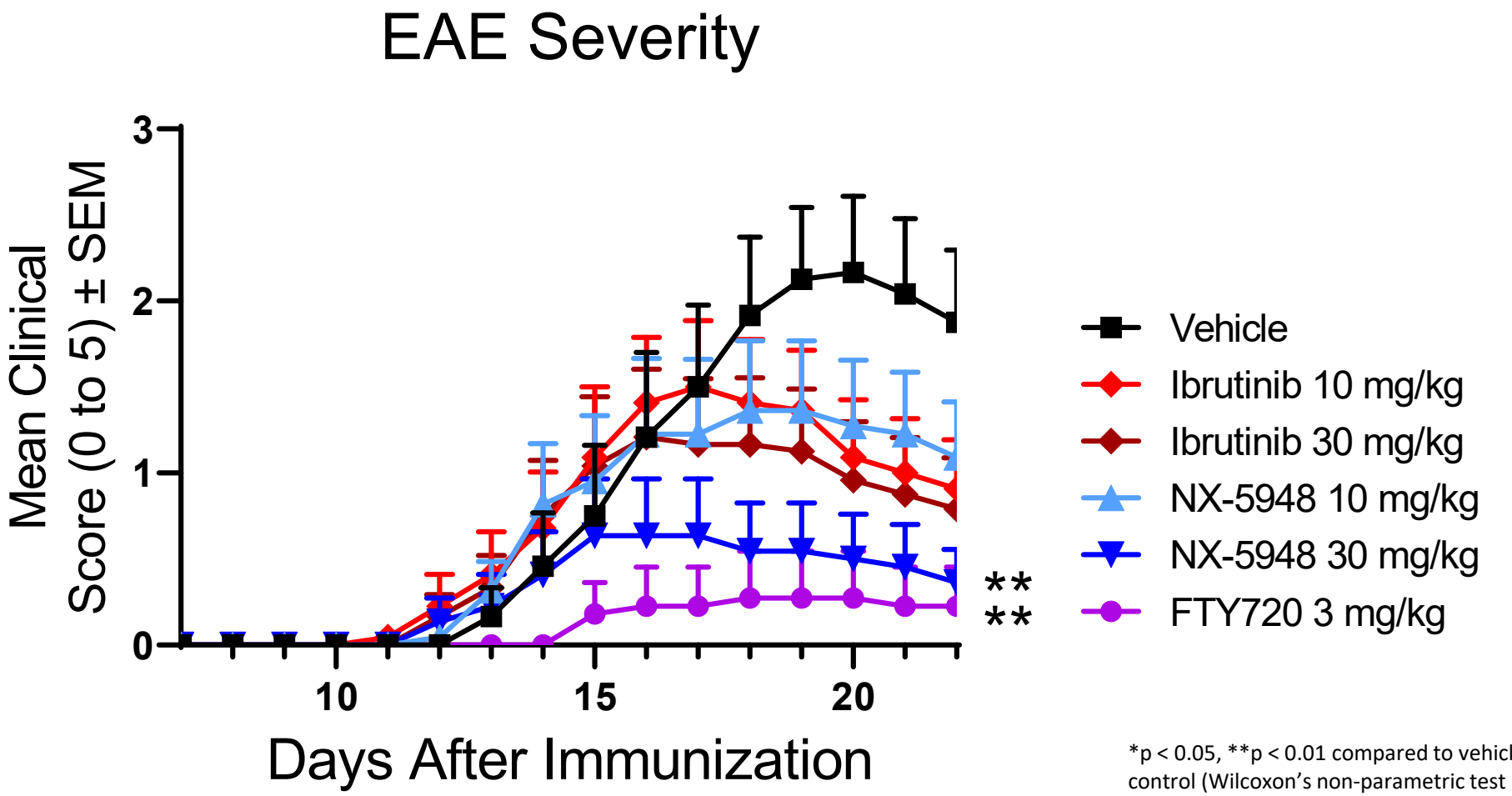
Rat plasma protein binding = 98.4%



*One of three CSF samples collected at 24 h was excluded as an outlier based on criteria defined by Motulsky et al., Detecting outliers when fitting data with nonlinear regression – a new method based on robust nonlinear regression and the false discovery rate. BMC Bioinformatics 7, 123 (2006).

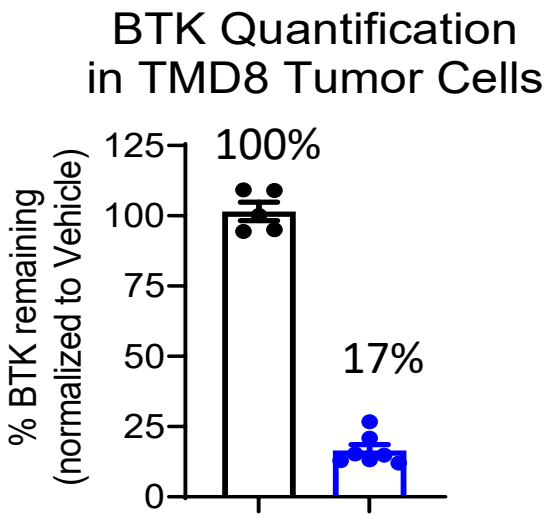
NX-5948 is Superior to Ibrutinib in Preclinical Model of CNS Disease

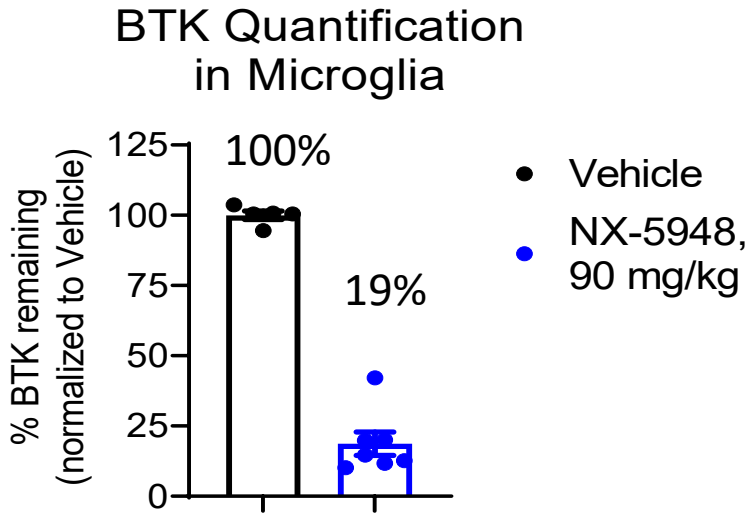
Experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis

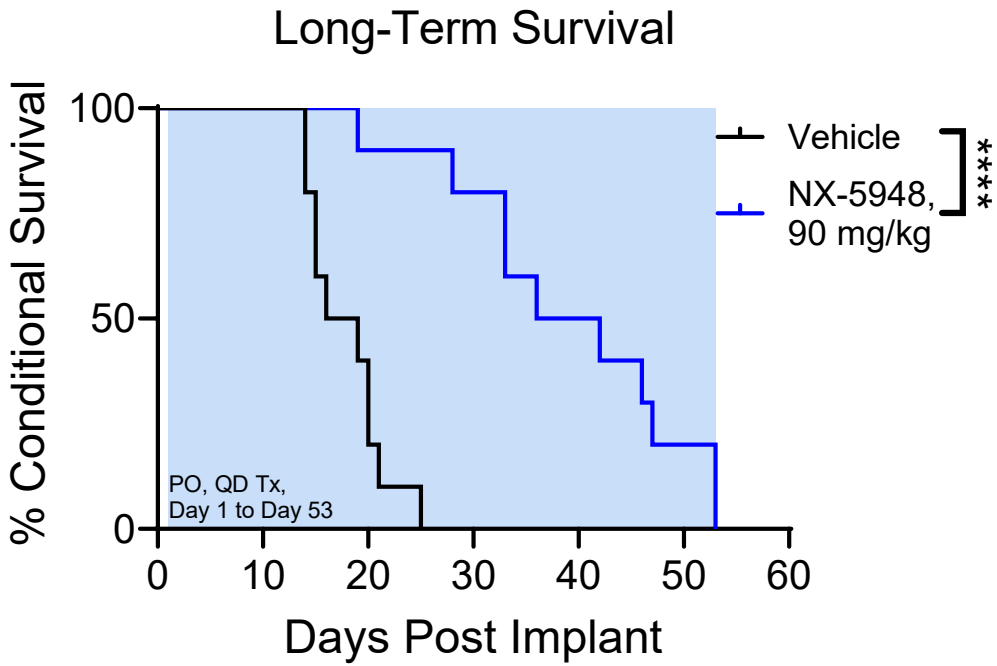


*p < 0.05, **p < 0.01 compared to vehicle control (Wilcoxon's non-parametric test on average end clinical score)

Daily Oral Administration of NX-5948 to Mice With Intracranial TMD8 DLBCL Tumors Degrades BTK in Brain-Resident Cells and Prolongs Survival



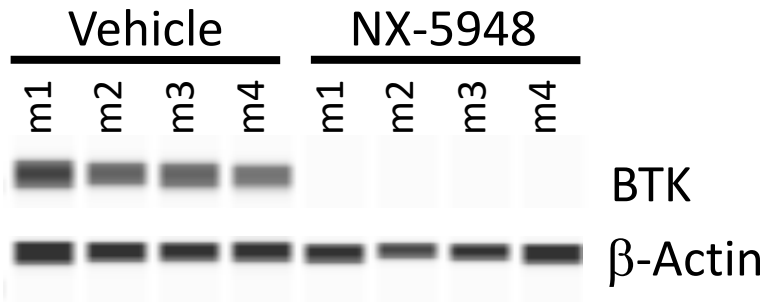


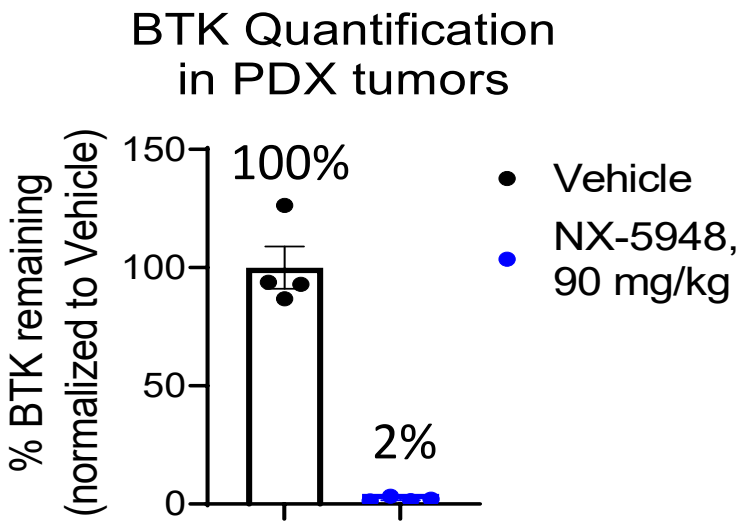


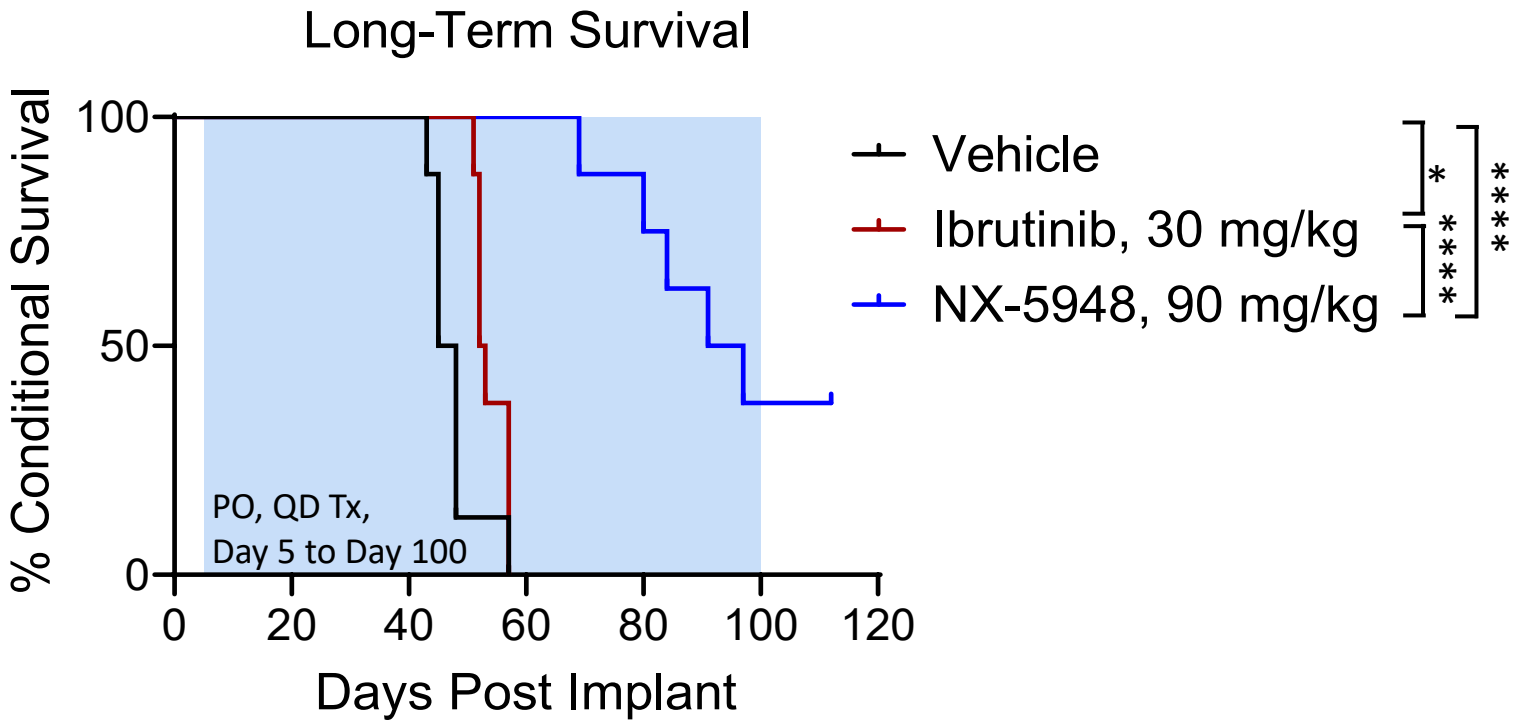
5 x 10^5 TMD8 cells implanted by intracranial injection on Day 0
NX-5948 administered orally QD Days 1-11 (left) or Days 1-53 (right)
BTK levels assessed 24 h after the 11^{th} dose by flow cytometry

****p < 0.0001 compared to vehicle control (Log-rank test)

Daily Oral Administration of NX-5948 to Mice Implanted with Intracranial DLBCL PDX Cells Drives Potent BTK Degradation and Prolongs Survival







SC1 cells are derived from a patient with highly refractory CD79b and EVT6-mutant large B-cell secondary CNS lymphoma, resistant to R-CHOP, high-dose methotrexate/rituximab, etoposide, Ara-C and irradiation.

Dr. James Rubenstein, MD, PhD, UCSF

CLL and NHL with CNS Involvement Remain an Area of High Unmet Need

- CNS involvement of B cell malignancies span various conditions including:

Primary CNS Lymphoma (PCNSL)
Comprises ~4% of all primary CNS tumors and 4-6% of all extranodal lymphomas[1]

Secondary CNS Lymphoma (SCNSL)
Affects ~5% of patients with DLBCL[2]

CNS involvement with CLL
Rare complication of CLL with dismal prognosis in patients with clinically significant disease[3]

- First-line standard of care typically involves high-dose methotrexate-based chemotherapy regimens with limited option in the relapse / refractory setting

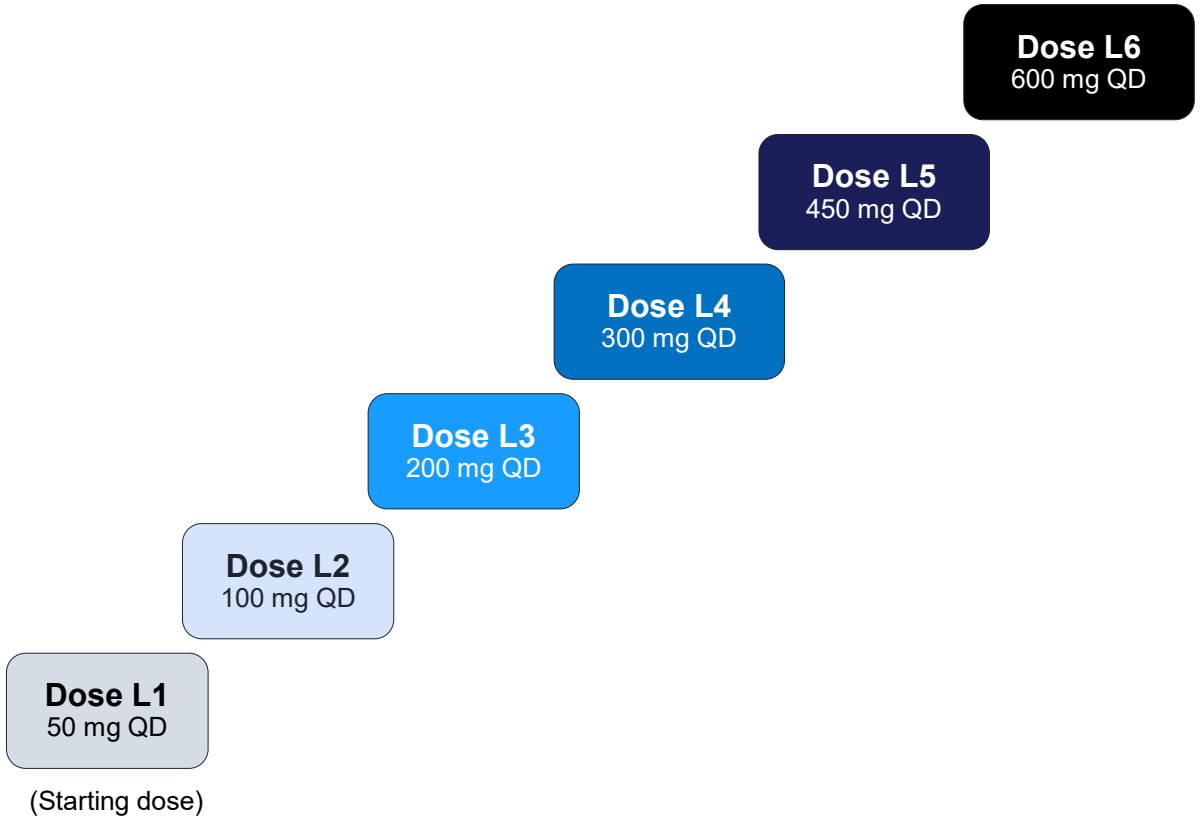
- Investigational drugs (BTKi, CAR-T, immune check point inhibitors) have been used in the relapse/refractory setting with some limitation including short duration of response and challenging safety profile

[1] *Ferreri et al. Nat Rev Dis Primers. 2023 Jun 15;9(1):29.*
[2] *Bobilla et al. Haematologica. 2023 Mar 1;108(3)*
[3] *Strati P. et al. Haematologica. 2016 Apr; 101(4)*

Phase 1 Trial of NX-5948 in Adults With Advanced B-cell Malignancies

Only BTK Degrader trial to permit patients with CNS involvement at baseline

Phase 1a dose escalation
B-cell malignancies (N = up to 66 CLL and up to 66 NHL/WM)



Potential Phase 1b dose expansion
(N = up to 160 patients)

CLL/SLL dose level A Prior BTKi and BCL-2i	**CLL/SLL dose level B** Prior BTKi and BCL-2i

MCL[a]
Prior BTKi and anti-CD20 CIT

MZL[a]
Prior anti-CD20 CIT and ≥2 prior LoT

WM[a]
Prior BTKi and ≥2 prior LoT

DLBCL[a,b]
Prior anthracycline, anti-CD20 CIT + 1 LoT[c]

FL
Prior anti-CD20 CIT + 1 LoT[c]

PCNSL/SCNSL
Who have progressed or had no response to ≥1 prior LoT

[a]Includes patients with secondary CNS involvement; [b]Subtypes include: transformed indolent lymphoma (e.g., grade 3b/transformed FL), Richter-transformed DLBCL, high-grade B-cell lymphoma with MYC and BCL-2 and/or BCL-6 rearrangements, high-grade B-cell lymphomas NOS; [c]Additional lines of therapy include anthracycline for non-GCB DLBCL and BTKi for MCL

Baseline Demographics and Disease Characteristics

Heavily pretreated population

Characteristics	Patients with CLL (n=7)	Patients with NHL/WM (n=19)	Overall population (N=26)
Median age, years (range)	64.0 (53–75)	63.0 (42–79)	63.5 (42–79)
Male, n (%)	5 (71.4)	13 (68.4)	18 (69.2)
Female, n (%)	2 (28.6)	6 (31.6)	8 (30.8)
ECOG PS, n (%)			
0	1 (14.3)	5 (26.3)	6 (23.1)
1	6 (85.7)	14 (73.7)	20 (76.9)
Previous targeted treatments[a], n (%)			
BTKi	7 (100.0)	10 (52.6)	17 (65.4)
Pirtobrutinib	1 (14.3)	2 (10.5)	3 (11.5)
BCL2i	6 (85.7)	3 (15.8)	9 (34.6)
BTKi and BCL2i	6 (85.7)	3 (15.8)	9 (34.6)
CAR-T therapy	0 (0.0)	7 (36.8)	7 (26.9)
Bispecific antibody	0 (0.0)	5 (26.3)	5 (19.2)
PI3Ki	2 (28.6)	2 (10.5)	4 (15.4)
Median prior lines of therapy (range)	3.0 (2–5)	5.0 (2–10)	4.0 (2–10)
Mutation status[b], n (%)	n=6	n=15	n=21
BTK (T474)	1 (16.7)	0 (0.0)	1 (4.8)
PLCG1/2[c]	2 (33.3)	2 (13.3)	4 (19.0)
TP53	2 (33.3)	3 (20.0)	5 (23.8)
BCL2 (G101V and R107-R110dup)	2 (33.3)	0 (0.0)	2 (9.5)

[a]Patients could have received multiple prior treatments; [b]Patients could have multiple mutations, which were tested at baseline by central NGS (≥5% allelic frequency is reported); [c]*PLCG1 (A902V); PLCG2 (K35R, V886A, V105I)*

Data cutoff: 17 Oct 2023

Searle E, et al. Blood 2023;142(Suppl 1):4473

NX-5948 Was Well Tolerated

Frequency of TEAEs in ≥15% of patients or grade ≥3 or SAEs in >1 patient, (n=26)

TEAEs, n (%)	Any grade	Grade ≥3	SAEs
Purpura/contusion[a]	12 (46.2)	–	–
Thrombocytopenia[b]	10 (38.5)	2 (7.7)	–
Neutropenia[c]	8 (30.8)	5 (19.2)	–
Anemia	6 (23.1)	1 (3.8)	–
Cough	5 (19.2)	–	–
Headache	5 (19.2)	–	–
Nausea	5 (19.2)	–	–
Rash	4 (15.4)	–	–
COVID-19	3 (11.5)	2 (7.7)	2 (7.7)
Pneumonia	2 (7.7)	2 (7.7)	2 (7.7)

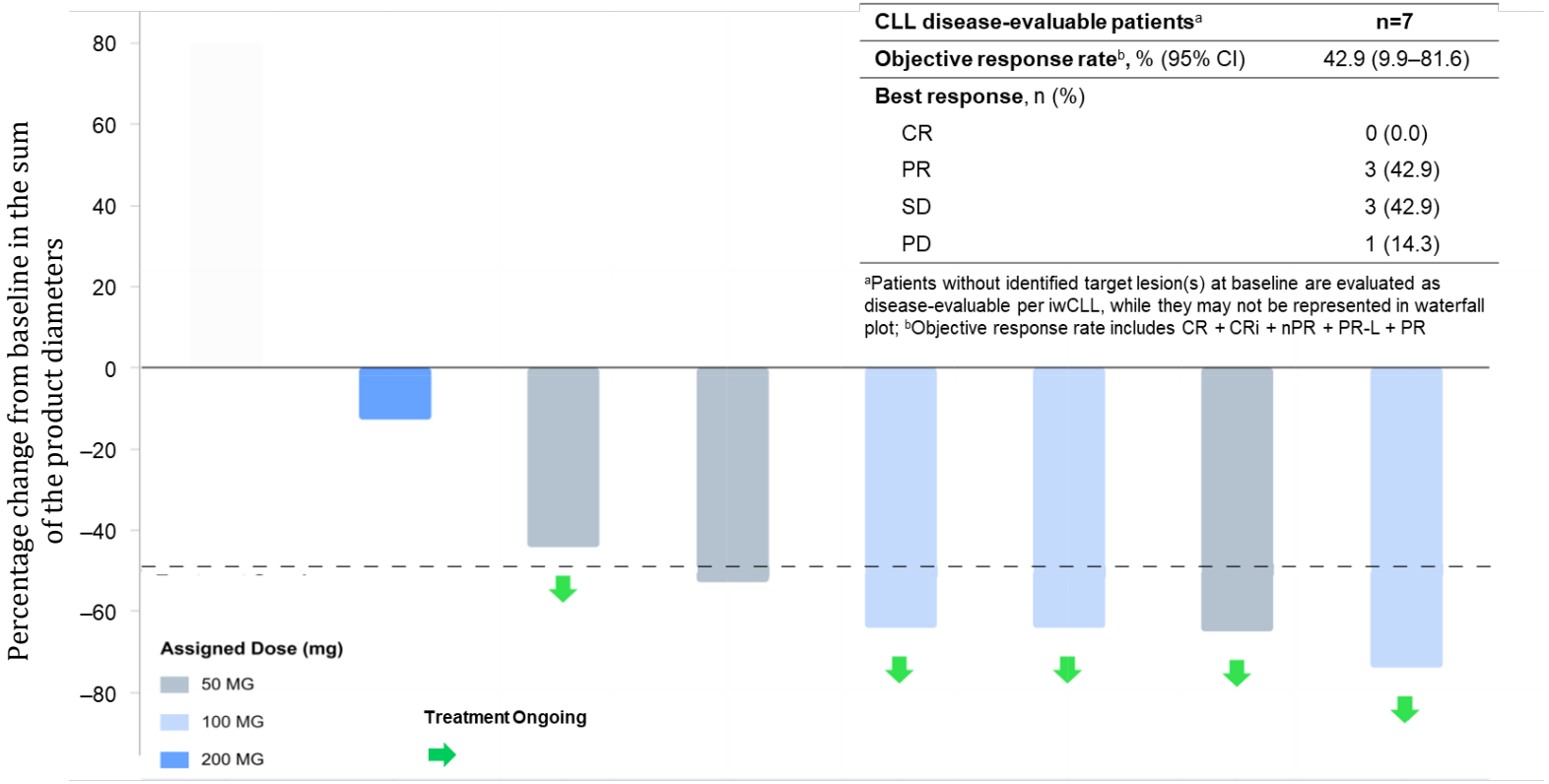
[a]Purpura/contusion includes episodes of contusion or purpura; [b]Aggregate of 'thrombocytopenia' and 'platelet count decreased'; [c]Aggregate of neutrophil count decreased or neutropenia

- **No atrial fibrillation/flutter or hypertension**
- **No DLTs and no TEAEs resulting in drug discontinuation**
- **Four NX-5948-related grade ≥3 TEAEs (3 neutropenia, 1 thrombocytopenia); no related serious adverse events**

Data cutoff: 17 Oct 2023

Searle E, et al. Blood 2023;142(Suppl 1):4473

Positive Initial Findings in Heavily Pretreated CLL Patients



CLL disease-evaluable patients[a]	n=7
Objective response rate[b], % (95% CI)	42.9 (9.9–81.6)
Best response, n (%)	
CR	0 (0.0)
PR	3 (42.9)
SD	3 (42.9)
PD	1 (14.3)

[a]Patients without identified target lesion(s) at baseline are evaluated as disease-evaluable per iwCLL, while they may not be represented in waterfall plot; [b]Objective response rate includes CR + CRi + nPR + PR-L + PR

CI, confidence interval; **CLL**, chronic lymphocytic leukemia; **CR**, complete response; **PD**, progressive disease; **PR**, partial response; **SD**, stable disease

Data cutoff: 17 Oct 2023

Next clinical update anticipated in mid-2024

SPD, sum of the product of diameters; iwCLL, international Workshop on CLL

Conclusions:

- NX-5948 PK exposure resulted in rapid, robust, and sustained BTK degradation
- NX-5948 was well tolerated at all doses tested
- Meaningful clinical benefit in CLL patients
  - 6/7 patients showed clinical benefit
    (3 PRs all ongoing, 3 SD with 2 ongoing)
  - All patients had evidence of lymph node reduction
- Durable responses observed in NHL/WM with data at higher doses anticipated mid-year

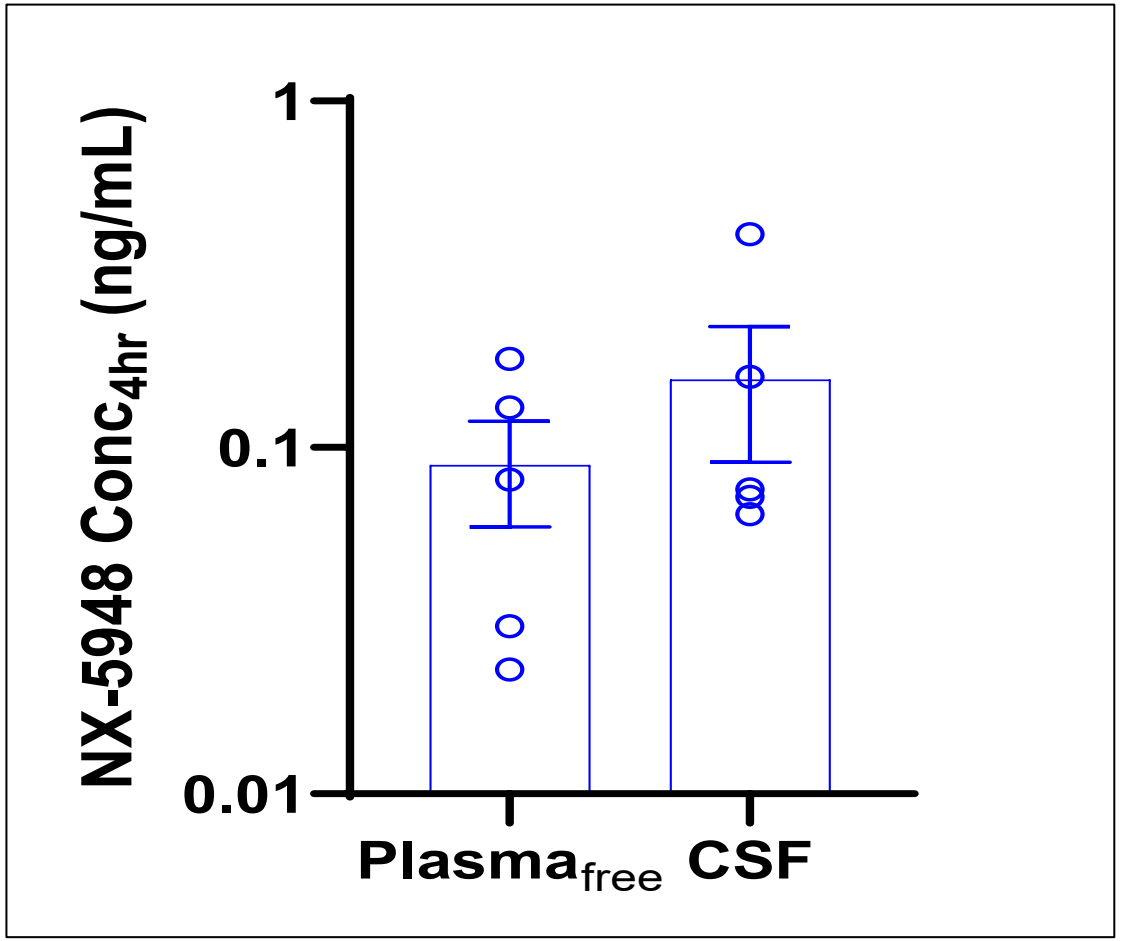
Data cutoff: 17 Oct 2023

Searle E, et al. Blood 2023;142(Suppl 1):4473

Detectable Levels of NX-5948 in CSF of Patients With CNS Involvement

As of Jan 16, 2024:

- Six patients with CNS involvement (1 CLL, 5 NHL) were enrolled
- 5 patients with available PK data



LLOQ: 0.01ng/mL(CSF); 0.1ng/mL(total plasma)

NX-5948 in Patients with NHL and CLL With CNS Involvement

Two Case Reports

	Patient #1	Patient #2
Disease	**PCNSL**	**CLL with CNS involvement**
Age, M/F	65, F	58, M
Dose	450 mg QD	100 mg QD
Time on Study*	Off Treatment, @ 16wk assesment	Ongoing, Cycle #10 (>36wks)
Prior lines of tx	2	3
Prior BTKi?	Yes (ibrutinib)	Yes (acalabrutinib)
CSF PK (Y/N)	Y	Y

*As of: data extract March 4, 2024

First Case Study: PCNSL

Multiple lines of prior therapies including cytotoxic chemotherapy and BTK inhibitor

Patient demographics and disease characteristics

- 65-year-old female with PCNSL
- Initial Diagnosis: Oct 2021

Prior treatments

1. Cytotoxic chemotherapy: Oct 2021 – Feb 2022 (CR)
    - Induction: Methotrexate, TMZ + R
    - Consolidation: High dose Ara-C
2. Ibrutinib: June 2022 – Sept 2023 (SD)

Relevant medical history

- Hypertension, Feb 2023
- Purpura, 2021

Molecular and cytogenetic features (from history)

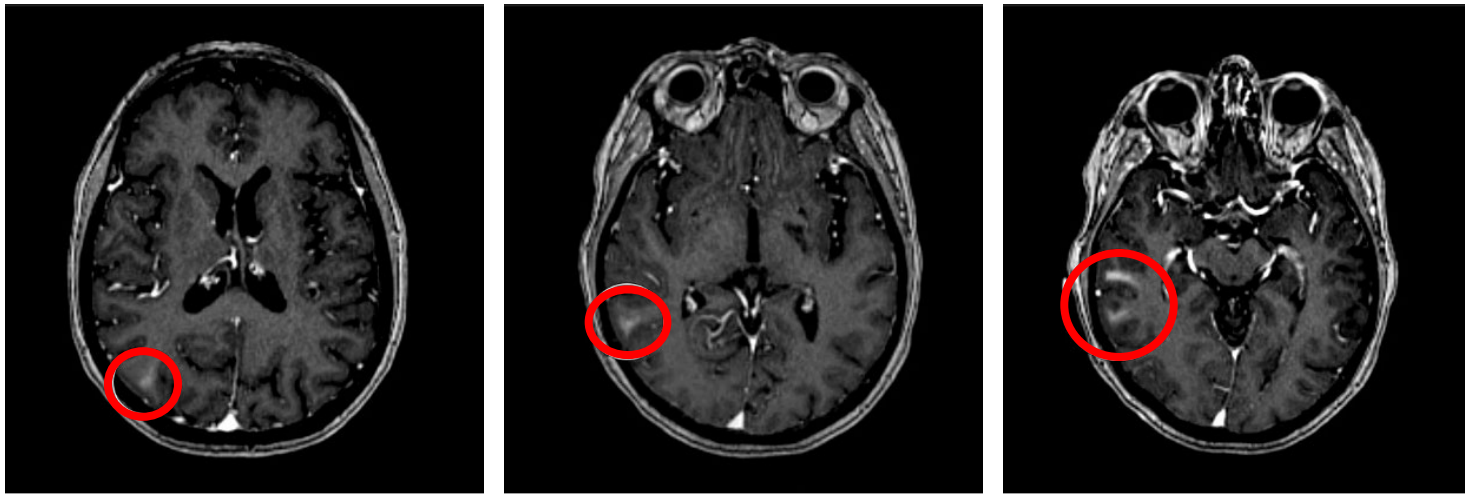
- MYC rearrangement
- MYC and BCL2 ICH +

Safety	
Exposure	No dose interruptions or dose modifications
DLT's	None
SAE's	None
Grade 3 or > AE	Gr3 HTN All other TEAEs Gr 1 or 2

*As of: data extract March 4, 2024

First Case Study: PCNSL

Pretreatment



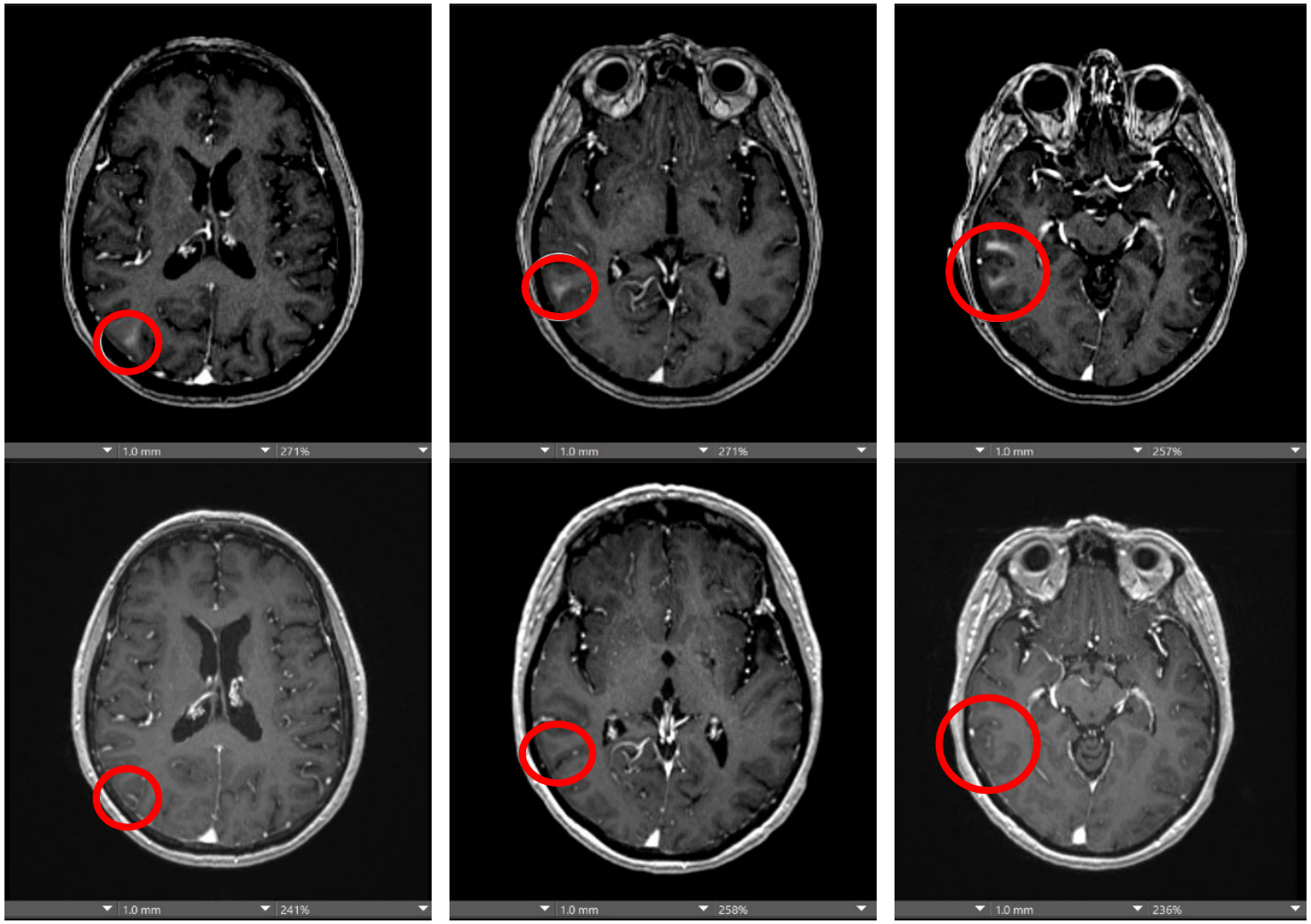
Pretreatment:
3 contrast enhancing lesions in the right temporal lobe

First Case Study: PCNSL

Complete Response observed at 8 weeks

Pretreatment

8 weeks

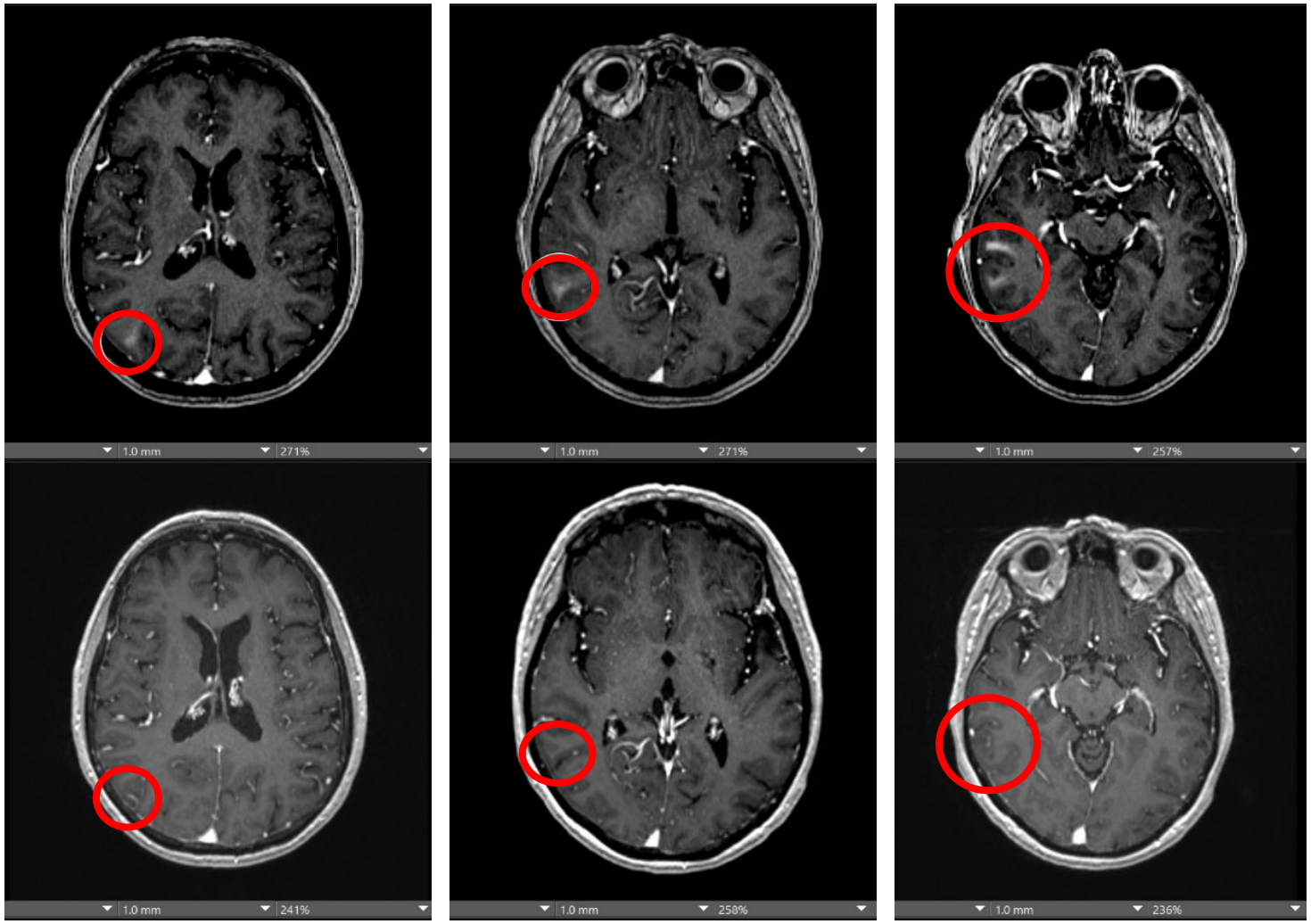


Pretreatment:
3 contrast enhancing lesions in the right temporal lobe

8 weeks: Complete Response
Complete resolution of all temporal lobe lesions

First Case Study: PCNSL

Complete Response observed at 8 weeks



Pretreatment:
3 contrast enhancing lesions in the right temporal lobe

8 weeks: Complete Response
Complete resolution of all temporal lobe lesions

16 weeks: Progressive Disease
New lesions

Second Case Study: CLL With CNS Involvement

Multiple lines of prior therapies including BTK inhibitor

Patient demographics and disease characteristics

- 58-year-old male with CLL
- Initial CLL diagnosis: 2015
- CNS disease diagnosis: May 2023

Prior treatments

1. Idelalisib: 2015 – 2018
2. Venetoclax-Rituximab: 2018 – 2022
3. Acalabrutinib: 2022 – June 2023

Relevant medical history

- Facial numbness
- Shingles

Molecular and cytogenetic features (from history)

- Del (17p)

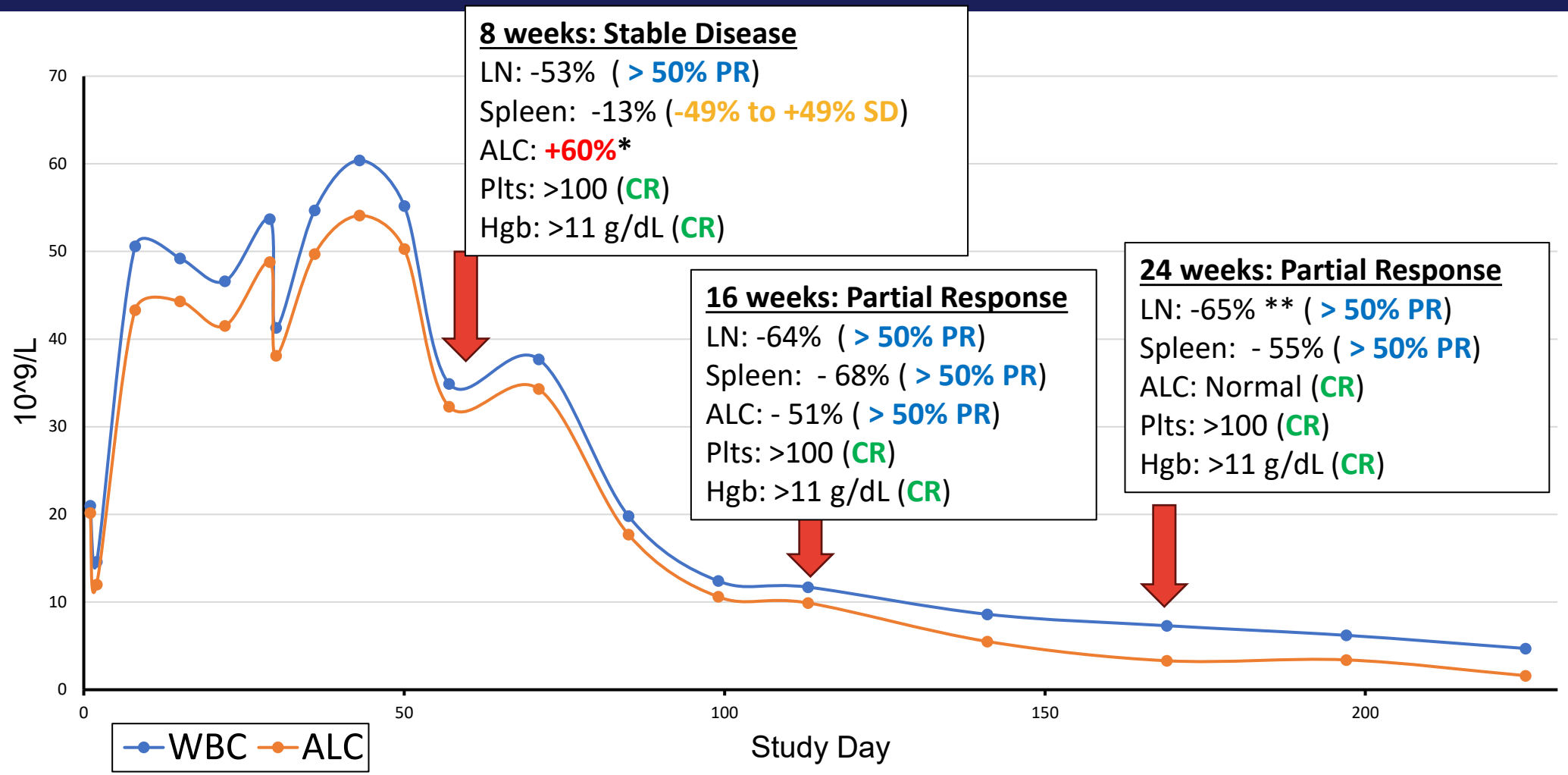
Safety	
Exposure	Dose interruptions (infections)
DLT's	None
SAE's	None

Grade 3 or > AE	• Baseline Gr4 Neutropenia
	  • Managed with intermittent GCSF which required increased frequency during cycle 1
	  • ANC normalized beginning C6D1 *
	• Two unrelated Gr 3 infections : PICC line infection and RSV
	• All other related AEs Gr 1 or 2

*Cycle 10 as of data extract March 4, 2024

Second Case Study: CLL With CNS Involvement

Early clinical activity deepening over time



*Initial lymphocytosis consistent with BTK targeted MOA.**Only 1 LN > 1.5cm
The overall response assessments are from the investigators while the individual parameter response assessment criteria are calculated per iwCLL from the data entered.

Data extract Date: March 4, 2024

Second Case Study: CLL with CNS Involvement

Timing of CSF clearance correlates with overall clinical response

	Screening	Week 8	Week 16	Week 24
Extra-CNS response	-	Stable Disease	Partial Response	Partial Response
CSF RBC (cells/mm^3)	63	522	65	82
CSF WBC (cells/mm^3)	173	63	28	18
Presence of malignant cells in the CSF	Yes	Yes	Yes	No

Data Cut Date: March 4, 2024

Targeted Protein Degrader NX-5948 Has the Potential to Address B-Cell Malignancies, Including Those With CNS Involvement

Targeted protein degradation can provide therapeutic benefit beyond what can be achieved with small molecule inhibitors

- Degraders can target known and novel clinical resistance mutations
- Unlike an inhibitor, a degrader can address both the enzymatic and scaffolding functions of a protein
- Degraders can achieve effective target coverage with much lower drug exposure

Despite falling outside the physicochemical property space established for CNS penetrant drugs, NX-5948 demonstrates CNS exposure

- In rat, CSF exposure is similar to unbound plasma exposure
- Degradation of BTK confirmed in microglia following once daily dosing in rat
- Efficacy superior to Ibrutinib observed in models of multiple sclerosis and CNS DLBCL

NX-5948 is well-tolerated with no dose limiting toxicities and no treatment emergent adverse events resulting in drug discontinuation

CSF exposure and clinical activity observed in both PCNSL and CLL with CNS involvement, despite multiple prior lines of treatment including BTKi

The NX-5948-301 study is actively enrolling patients in the US, UK and the Netherlands

- Additional data with higher dose levels and longer treatment duration are expected mid-2024

Acknowledgements

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